Guidance for Serious Adverse Events and Unanticipated Problems

The IRB requires reporting of Serious Adverse Events and Unanticipated Problems as they arise during the conduct of research. There may be alternate definitions or additional reporting associated with such events, depending on the nature of funding or oversight. It is critical that researchers understand these definitions and reporting requirements prior to the conduct of research.

1. What is a Serious Adverse Event (SAE)?

An Adverse Event is an any physical or psychological harm experienced by a participant in human subjects research, whether or not considered related to the subject's participation in the research. A Serious Adverse Event is any Adverse Event which includes one or more of the following outcomes:

- Is fatal or life-threatening.
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly or birth defect.
- May jeopardize the subject's health.
- Any serious psychological and emotional distress resulting in study participation (suggesting need for professional counseling or intervention).

A Serious Adverse Event is defined and reported as either:

- Internal, in that it occurred during research conducted under the oversight of the Lindenwood University IRB.
- External, in that it occurred in research conducted outside of, but is related to, research conducted under the oversight of the Lindenwood University IRB. For example, Lindenwood University may be participating in a multi-site study. If an SAE occurs in a subject enrolled at a different site, the even would be considered External.

2. What is an Unanticipated Problem (UP)?

Unanticipated Problems are referenced in 45 CFR 46 as "unanticipated problems involving risks to subjects or others". Federal regulations require institutions engaged in human subjects research to have written procedures for ensuring prompt reporting of Unanticipated Problems to the IRB. This procedure will include reporting of Unanticipated Problems to the Office for Human Research Protections when necessary. Researchers at Lindenwood University are expected to know that funding agencies and sponsors may have reporting requirements in addition to those outlined by this policy.

- While 45 CFR 46 does not provide a specific definition of an Unanticipated Problem (UP), the Office for Human Research Protections (OHRP) considers a UP to include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

- The IRB will make a determination on a case by case basis as to whether an event constitutes an Unanticipated Problem. According to OHRP guidance, examples of UPs include:

  - An accidental or unintentional change to the IRB approved protocol that placed one or more participants at increased risk, or has the potential to occur again.
  - A change to the protocol made without prior IRB review to eliminate an apparent immediate hazard to a research participant.
  - Interim findings and/or a safety monitoring report that indicate an unexpected change to the risks or potential benefits of the research in terms of severity or frequency.
  - Publication in the literature that indicates an unexpected change to the risks or potential benefits of the research.
  - A complaint of a participant that indicates unexpected risks or that cannot be resolved by the research team.
  - Incarceration of a participant in the course of a study.
  - A change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
  - A breach of a participant's confidentiality or privacy that involves potential risk to that participant or others.

- There are cases in which Noncompliance (a Major or Minor Deviation from the approved protocol or applicable policy and procedures) should also be reported as an Unanticipated Problem.
- In cases of receipt of a complaint from a research subject, or prospective research subject, the Principal Investigator must contact the IRB as soon as possible for advice on responding appropriately.

3. What is the difference between an SAE and a UP?

Both Serious Adverse Events and Unanticipated Problems are events which may be experienced by participants or others during the conduct of human subjects research. The difference is that some Serious Adverse Events are anticipated, and are described or disclosed appropriately in protocols, IRB applications, and consent materials. An Unanticipated Problem is by definition unexpected, and therefore may not already been identified by the research team.

It is helpful to recognize that:

- The majority of adverse events occurring in research involving human subjects are not Unanticipated Problems.
- There are cases when an adverse event also meets the definition of an Unanticipated Problem.
- Not all Unanticipated Problems are also adverse events, as they include any experience or incident which meets the definition of a UP.
- Unanticipated Problems are not limited to clinical research and can occur in any discipline of research or type of research design.

4. When is a SAE also potentially a UP?

OHRP recommends that IRBs and researchers use the following questions to determine if an adverse event is an Unanticipated Problem. If the answer to the following three questions is yes, then the adverse event must be reported as an Unanticipated Problem:

- Is the adverse event unexpected?
- Is the adverse event related or possibly related to participation in the research?
- Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

5. How does a researcher report SAEs or UPs?

All Serious Adverse Events and Unanticipated Problems must be reported to the IRB according to the timelines outlined below. Researchers must complete a Reportable Event Form and submit this form as a "Reportable Event" in Cayuse IRB for review by the IRB. The Lindenwood University IRB may require modifications to the approved study and/or initiate a Corrective Action Plan (CAP) to ensure ongoing protections for participants and others.

6. What are timelines for reporting SAEs or UPs?

The IRB expects researchers to adhere to the following timelines, unless an agency or sponsor requires a shorter timeline:

Event or Process	Time in Calendar Days
Reports of Serious Adverse Events or Unanticipated Problems	7
Reports of Subject Complaints	1
Reports of life-threatening Serious Adverse Events	1 (Internal) / 3 (External)
Reports of Adverse Events	At Continuing Review
Reports of Noncompliance	7
Reports of Safety Alerts or New Information	7
External Event or Safety Reports	7
Audit Notifications or Reports	14